Transduction of membrane tension by mechanosensitive ion channels. Wade J. Sigurdson and Fred Sachs. Department of Biophysical Sciences, SUNY at Buffalo, Buffalo, NY, 14214.

Mechanotransduction is an essential component of cellular sensory mechanisms, being important not only for sensing of external stimuli, but also in internal regulatory mechanisms at the cellular and organ level. Mechanosensitive (MS) ion channels are ideal candidates for the primary transduction event, ie. the sensing of membrane tension. These channels have been found in prokaryotes, plants, fungi and all animal phyla so far studied, thus implying a primary function in the physiology of many organisms. The channels have been studied almost exclusively using single-channel recording and have shown varying ionic selectivities; the most common being cation selective, while others are K^+ or anion selective. Modes of channel gating include stretch-activation (SA) and stretch-inactivation (SI). The channels can be stimulated by both positive and negative pressure indicating changes in membrane tension is the primary stimulus. Capacitance measurements suggest tension is not carried by the lipid, but by underlying cytoskeletal components in which MS channels maybe in series. Thus mechanical energy sufficient for gating MS channels would be transmitted to MS channels via a cytoskeletal network consisting of perhaps spectrin. The model of channel gating proposed by Sachs and Lacar submits that channel gating is dependent on a linear and a quadratic force term. The compliance (spring constant) of the channels open and closed states determines the magnitude of the quadratic term and predicts that the opening rate will be tension-insensitive if the open state is stiffer than the closed state. This appears to be the case in cation selective channels whose kinetics have been closely studied. A direct demonstration of a physiological role for SA or SI channels has been hampered by the lack of specific pharmacological agents which block channel function. Mechanically activated whole-cell currents have been shown in yeast and smooth muscle countering the report of failure to elicit such currents in molluscan neurons. To address this problem without invoking the use of electrical measurements, we employed the Ca^{2+}-binding fluorescent dye FLUO-3 in embryonic chick cardiac myocytes. Cells spontaneously beating showed correlated changes in fluorescence intensity, thus providing a physiological baseline for any mechanically induced Ca^{2+} changes. Prodding these cells with a blunt probe initiated a wave of increased florescence that spread throughout the cell. A similar response could be obtained by indirect stimulation of a cell by the movement of its neighbour. The total Ca^{2+} flux through the SA channels is not sufficient to produce the large intracellular Ca^{2+} increase observed. Instead, we feel that a localized Ca^{2+}increase initiates Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum. The response was blocked by removal of external Ca^{2+} and by 20 μM Gd^{3+}. 20 μM gadolinium also blocks the cation-selective SA channel in these cells. This approach should be useful for screening pharmacological agents which interfere with SA channel function. Moreover, it has provided evidence for a physiological role for mechanosensitive channels.

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